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Role of Serum Ca 125 Level in the Diagnosis of Pulmonary Tuberculosis

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I. Introduction

1.1 Introduction

Pulmonary infection with tubercular bacilli remains one of the leading causes of mortality worldwide and has become a global public health emergency (Rajasekhar, 2017). The World Health Organization estimates that each year more than 8 million new cases of tuberculosis occur and approximately 3 million persons die from the disease. Ninety-five percent of tuberculosis cases occur in developing countries (Fortun *et al.*, 2009). TB currently holds the seventh place in the global ranking of causes of death. Unless intensive efforts are made, it is likely to maintain that position through to 2020 (Mohammad *et al.*, 2016).

Exact and early diagnosis of tuberculosis is important, as untreated disease may be fatal in 05 years in more than half of cases. Although several diagnostic tests have been developed for accurate diagnosis and evaluation of pulmonary infection but diagnostic facility for distinction of pulmonary TB infection from other non-tubercular pulmonary infection and evaluation of therapeutic responses is not common (Said *et al.*, 2013;Mohammad *et al.*, 2016; Mikačić et al., 2017). Microscopic examination of acid fast stained sputum smears remain the most useful diagnostic method and positive samples establish indications for initiation of TB therapy and respiratory isolation. In high prevalence of TB areas, the sputum smear microscopy test, with a sensitivity of 50% - 70%, is available and affordable. Although smear negative cases are less infectious than smear positive cases, at least 17% of TB cases are affected by smear negative cases (Fortun *et al.*, 2009; Rajasekhar, 2017).

PCR test has found an increasingly wide utilization in TB diagnosis, but in developing areas its utilization remains limited because of the high cost of detection and the deficiency of special equipment and professional staffs. However, in some cases of pulmonary TB, acid-fast bacilli stains in sputum samples may be negative or respiratory specimens may not be available, and other methods have to be used to establish the diagnosis of TB. In clinical practice it is very difficult to discriminate active tuberculosis from inactive TB case for commencing anti TB therapy in time. Apart from microbiological molecular diagnostic tests, different biochemical parameters have been proposed as helpful tools for this purpose, including various markers of cellular activity, acute phase reactants and enzymes (Fortun *et al.*, 2009; Rajasekhar, 2017). The tumor marker Cancer antigen 125 has been proposed as a useful diagnostic tool for tuberculosis. (Fortun *et al.*, 2009; Said *et al.*, 2013; Rajasekhar, 2017).

Cancer antigen 125 or carbohydrate antigen 125 is a high molecular weight glycoprotein (200 KDa) that is expressed on the epithelial cells of the fallopian tube, endometrium, and mesothelial cells lining the pleura, pericardium and peritoneum. CA 125 levels are elevated in a number of malignant diseases such as those involving the ovaries, lungs, breasts, colon, pancreas, and in some non-malignant conditions including endometriosis, hepatic cirrhosis or heart failure (Mohammad et al., 2016; Mikačić et al., 2017).

If destruction of these cells occurs due to inflammation or tumor, CA 125 will be released and increased in the serum. In pulmonary TB, it was claimed that raised levels of Ca 125

can greatly increase the likelihood of tuberculosis activity (Ozsahin et al., 2008; WHO, 2014). The diagnostic value of Ca-125 to help differentiate pulmonary tuberculosis from other pulmonary infections has been poorly studied (WHO, 2004; Ozsahin et al., 2008; WHO, 2014).

Yilmaz and colleagues (Yilmaz et al. 2001) found that CA 125 in serum had 97.5% sensitivity and 100% specificity in discrimination active from inactive pulmonary tuberculosis (Ozsahin *et al.*, 2008; Mikačić *et*

al., 2017). Information pertinent to diagnostic role of tumor markers is insufficient. The present study was undertaken to ascertain the role of serum CA 125 level in the diagnosis of pulmonary tuberculosis.

1.2 Rationale of the study

It is important to make a confirmed diagnosis of TB to timely initiate anti tubercular therapy to prevent morbidity and mortality. Often, it is difficult to make a confirmed diagnosis due to lack of adequate sample materials or investigation faicility like X- pert MTB/RIF machine to test for tuberculosis, especially in patients with hemoptysis or smear negative pulmonary tuberculosis. Thus, many times patients are undertreated or lately treated as these patients are misdiagnosed as non-tuberculosis chest infection or malignancy. Again, some are over treated as many of these patients are given therapeutic trial of anti TB drugs. So, we are in a need of a new cost effective, easy to do laboratory test to predict or confirm the diagnosis of TB in the absence of adequate test materials. The tumor marker serum CA 125 can be a valuable diagnostic tool of tuberculosis. So far, no known study is established in Bangladesh yet. Therefore, I like to find the role of serum CA 125 in the diagnosis of pulmonary tuberculosis.

1.3 Hypothesis:

Serum CA 125 level is a useful diagnostic tool for pulmonary tuberculosis.

1.4 Objectives of the Study

General objective:

To evaluate the role of serum CA 125 level in the diagnosis of pulmonary tuberculosis.

Specific objectives:

- To assess the level of serum CA 125 level of the participants
- To find out the presence of acid-fast bacilli in the sputum of PTB patients
- To find out the smear negative gene X-pert positive cases of PTB
- To compare the serum CA 125 level with sputum positive cases
- To compare the serum CA 125 level with gene X-pert positive cases

1.5 Operational Definitions

- **Pulmonary Tuberculosis:**

A patient with Mycobacterium tuberculosis complex identified from a clinical specimen either by microscopy or by culture or by a newer method such as X pert MTB/RIF, molecular line probe assay or a patient diagnosed by registered medical practitioner or by clinicians on basis of clinical feature or X ray findings and has decided to treat the patient with a full course of TB treatment is considered as a case of Pulmonary Tuberculosis (Chan, Heifets and Iseman, 2000).

- **Smear Positive Pulmonary TB:**

A patient with at least one sputum specimen positive for AFB, including any scanty smear result (WHO, 2011).

- **Smear Negative X pert MTB/RIF Positive Pulmonary TB:**

A patient with symptoms suggestive of TB with two sputum specimens negative for AFB, and found positive on X pert MTB+/RIF- (MTB detected Rifampicin Susceptible) (WHO, 2011)

- **Active Pulmonary Tuberculosis (TB Disease):**

Around 10% of the people infected with TB bacilli may progress to TB disease in their lifetime. TB bacilli multiply in their lungs or other organs and produce the symptoms and signs, Active TB means TB infection plus presence of signs and symptoms of TB.(WHO,2011)

- **CA 125**

CA 125 is glycoprotein with a high molecular weight, mucin-like, exists on the surface of ovarian, and some inflammatory and non-inflammatory cells like pleural cells. Proliferation of these cells causes this antigen to be released in serum.CA-125 was first known as a specific tumor marker that is the basis for a widely used serum assay for the monitoring of the ovary. Gradually it
was found that inflammation even without polymorphism (as in the early stage of pregnancy, menstrual cycle, PID, and endometriosis) causes this tumor marker to increase. Increased CA-125 levels in response to tuberculosis were first observed in 1980's. Later, it was revealed that tuberculosis in various sites of the body causes increase in serum Antigen level .The normal value of CA 125 –(0-35 U/ml) (ISTC, 2009; Mohammad *et al.*, 2016).

- **Socioeconomic status (SES):**

SES is an economic and sociological combined total measure of a person's work experience and of an individual's or family's economic and social position in relation to others. When analyzing a family's SES, the

household income, earners' education, and occupation are examined, as well as combined income, whereas for an individual's SES only their own attributes are assessed. However, SES is more commonly used to depict an economic difference in society as a whole.Socioeconomic status is typically broken into three levels (high, middle, and low) to describe the three places a family or an individual may fall into. When placing a family or individual into one of these categories, any or all of the three variables (income, education, and occupation) can be assessed.(American Psychological Association,2012)

II. Literature Review

Tuberculosis (TB) is one of the major global health problems leading to morbidity and mortality. TB pose as a huge threat to economic development as around 90% of TB-related deaths occur among productive age groups (Agyeman and Ofori-Asenso, 2017). Due to its public health importance TB control strategy is included in both Millennium Development Goals (MDGs) and Sustainable Development Goals (SDGs). Over the past decade, significant progress has been made towards TB control program set as part of the MDGs. End TB strategy with targets is included in newly adopted SDGs. Reduce TB deaths by 90% by 2030 as well as achieve an 80% reduction in TB incidence rate compared with 2015 is the target (WHO, 2014).

Tuberculosis:

Tuberculosis is a communicable infectious disease caused by the Mycobacterium tuberculosis. Mycobacterium Tuberculosis is aerobic, non-spore forming, non-motile bacillus. TB transmits almost exclusively by cough aerosol and characterized pathologically by necrotizing granulomatous inflammation (Dheda, Barry and Maartens, 2015). It usually affect in the lung (85% of cases). In 15–20% cases it affect outside the lung called extra pulmonary site. Extra pulmonary TB occurs more commonly in people with a weakened immune system and young children. Extrapulmonary infection sites include the pleura, the central nervous system, the lymphatic system, the genitourinary system, and the bones and joints. A potentially more serious, widespread form of TB is
called "disseminated tuberculosis", also known as miliary tuberculosis (Kala and Gauthaman, 2010).
Primary infection with M. tuberculosis leads to clinical disease in only 10% of individuals. It is termed as active TB. Active TB has a greater burden of TB bacilli than latent TB, and acts as an infection source for contacts (Ilievska-Poposka *et al.*, 2018). In the remaining cases, the ensuing immune response arrests the further growth of M. tuberculosis. However, the pathogen is completely eradicated in only 10% while the immune response in the remaining 90% individuals only succeeds in the containment of infection. This is termed as latent TB. Latent tuberculosis infection is the state in which humans are infected with M. tuberculosis without any clinical symptoms, radiological abnormality, or microbiological evidence. In this state patients are not infectious to others (Lee, 2016).

Epidemiology:

In 1993, WHO declared tuberculosis as a global emergency. One in three persons across the world (around 2–3 billion) are infected with Mycobacterium Tuberculosis of which 5–15% are likely to develop active TB disease (Agyeman and Ofori-Asenso, 2017). Each year approximately 8 million people develop active tuberculosis and 2 million die as a result of TB. It is the second leading cause of death from infectious diseases (Kala and Gauthaman, 2010). The incidence in high income countries is less than 10 per 100 000 population per year. But there are 30 high tuberculosis burden countries (which are

predominantly low-income and middle-income countries) where incidence is 183 per 100 000 population per year, with the incidence being above 400 per 100 000 population per year in eight countries. Tuberculosis burden is primarily borne by the poorest people (Furin, Cox and Pai, 2019).

Prevalence of TB is high in Asia. In Bangladesh, the population faces poverty, densely and poorly living and working situation, all of these facts allow more TB spread. Bangladesh is one of the highest TB burden countries accounting for one fifth of the global incidence of TB. It ranks sixth among the 22 high burden countries (*National Guide Lines-TB 5th Ed*, 2017). Over 300,000 people develop the disease every year of whom 70,000 die (Rahman, Giasuddin and Giasuddin, 2012). The WHO estimate of prevalence was estimated with a very large uncertainty at 434 /100,000

population for all types of TB. The estimated incidence remained stable for the last decade at 225 /100,000 per year. In 2012 around 2.8% children were affected by TB. Annual mortality rate from TB is also high, which is 45 per 100 000 population (*National Guide Lines-TB 5th Ed*, 2017). The disease is more prevalent in the productive age group of 15-54 years (Maruf Raza *et al.*, 2017). Bangladesh had comparatively higher percentage (81%) of notified cases of pulmonary TB that were sputum smear- positive among the 22 high burden countries. The prevalence of sputum smear-positive TB was found higher in the rural population (86.0/100 000) compared to urban ((51.1/100 000) in the recently completed (2007–2009) nationwide TB

prevalence survey of Bangladesh (Banu *et al.*, 2013). TB case notifications have increased significantly since 2012. At present the case notification rates of new smear positive TB have
increased significantly to a rate of 71/100,000 population in 2015 compared with 46/100,000 in 2004. The prevalence of multi drug resistance (MDR) cases among new cases was 1.4 % (0.7-2.5%), and among retreatment cases 29% (24-34%) (Das, 2017).

Risk factors: (Dheda *et al.*, 2015)

Several risk factors are associated with tuberculosis -

- poverty
- overcrowding
- under nutrition
- indoor air pollution
- alcohol misuse
- HIV
- silicosis
- chronic renal failure needing dialysis
- diabetes
- tobacco smoking and
- Immune-suppressive therapy.

Pathogenesis:

M. Tuberculosis is exposed to the air as droplet nuclei from coughing, sneezing, shouting or singing of individuals with pulmonary or laryngeal TB. These droplet nuclei passes through the mouth or nasal cavities, the upper respiratory tract, bronchi and finally reaches the alveoli of the lungs. In alveoli, they are ingested by alveolar macrophages

resulting in the destruction or inhibition of the tubercle bacilli (Schluger, 2005). The small unaffected proportion multiplies within the macrophages and is released upon death of the macrophages. Live released tubercle bacilli spread via the bloodstream or lymphatic channels to any part of the body tissues or organs (Smith, 2003). About 2 to 8 weeks an immune response is triggered which allows WBC to encapsulate or destroy majority of the tubercle bacilli. The encapsulation by the WBC results in a barrier around the tubercle bacilli forming a granuloma (Schluger, 2005). Inside the barrier shell, the tubercle bacilli is in a state of latent tuberculosis infection. Persons at this stage show no symptoms of TB, are unable to spread the infection. On the other hand, if the immune system fails rapid multiplication of the bacilli leads to a progression from latent to active TB (Agyeman and Ofori-Asenso, 2017).

Diagnosis:

Diagnosis of pulmonary TB is as important as early optimal treatment strategy. For a complete evaluation of TB following 5 point should be considered-

1. medical history taking
2. physical examination
3. test for M. Tuberculosis infection
4. chest radiograph and
5. bacteriologic examination of clinical specimens.

In the case of Pulmonary TB, this usually manifest as combination of one or more of the following symptoms; coughs (often lasting longer than 3 weeks with or without sputum

production), coughing up blood, chest pain, loss of appetite, unexpected weight loss, night sweats, fever and fatigue (Campbell and Bah-Sow, 2006).

Testing for M. Tuberculosis is achieved either through skin or blood tests. The skin test is known as Mantoux tuberculin test. Microscopic examination of acid-fast stained sputum smears remains the most useful diagnostic method. Smear microscopy has the benefit of being inexpensive with low technical requirements with a sensitivity of 50% - 70%. The most sensitive way of detecting M. tuberculosis is the culture on enriched media (Lowenstein–Jensen). This requires 6–8 weeks to rule out growth. Culture has increased sensitivity over AFB smear. It can also distinguish between non-tuberculous and tuberculous mycobacteria, which are indistinguishable on microscopy (Lawn, 2015).

Digital chest x-rays with computer-aided detection of tuberculosis have been increasingly used in various settings. Radiological changes would be compatible with pulmonary tuberculosis where sputum is negative on direct smear or culture. Typically upper lobe infiltrates or cavitary lesions is found in chest x-ray (Cudahy *et al.*, 2016).

Apart from these some newer techniques are also available for diagnosis. Interferon gamma release assays (IGRAs) were developed to find a more specific test that would not contain antigens used in TB vaccines. It can assess not only latent but also active tuberculosis. The most exciting development in TB diagnostics has been the use of polymerase chain reaction (PCR) for rapid diagnosis. PCR has the advantage of a turn-around time within hours, high specificity, and the potential for high sensitivity. But in developing areas its utilization remains limited because of the high cost of detection and

the deficiency of special equipment and professional staffs. More recently the Xpert MTB/RIF system has generated considerable interest. It is able to identify the presence of M. tuberculosis as well as multi-drug resistant (MDR) TB (Cudahy *et al.*, 2016).

Role of tumor marker in diagnosis:

Tumor markers play an important role in cancer detection and management. It is potentially useful in screening for early malignancy, aiding cancer diagnosis, determining prognosis, surveillance following curative surgery for cancer (Duffy, 2013). Usually multiple tumor markers are associated with individual malignancy such as -(Sharma, 2009)

- AFP is related with primary hepatocellular carcinoma, teratoblastomas of the ovary and testes.
- CEA is present in colorectal carcinoma
- CA 15-3 found in breast cancer
- CA 19-9 is associated with pancreatic and gastric carcinomas
- Beta-hCG in choriocarcinoma, testicular cancers (non-seminomatous), trophoblastic tumors
- Calcitonin in cancer of the thyroid, liver cancer, renal cancer
- CA-125 in ovarian carcinoma.

Tumor markers include a variety of substances like cell surface antigens, cytoplasmic proteins, enzymes, hormones, oncofetal antigens, receptors, oncogenes and their products. Detection can be done either in tissue or in body fluids like ascitic or pleural fluid or serum. Serum levels, in certain situations, can be used in staging, prognostication or prediction of response to therapy (Sharma, 2009). In clinical practice it is very difficult to discriminate active tuberculosis from inactive TB case for commencing anti TB therapy in time. Different studies proposed tumor marker CA-125 has role in diagnosis and determination of pulmonary TB activity.

Cancer antigen 125 (CA-125):

Cancer antigen 125 (CA-125) is a high molecular weight glycoprotein. CA-125 is primarily produced by amnion, fetal coelomic epithelium and its derivatives, but can also be produced by epithelial cells of the fallopian tube, endometrium, and mesothelial cells lining the pleura, pericardium, and peritoneum (Kim *et al.*, 2013). It is detected by the OC125 monoclonal antibody.

CA-125 is best known as a marker for ovarian cancer. Serum concentration of CA-125 is also known to rise in some benign and malignant diseases such as those involving the ovaries, lungs, breasts, colon and pancreas. CA125 used as a biomarkers for different types of cancers like- cancers of the endometrium, fallopian tube, breast, lung, and pancreas (Al-Ibraheemi, Dasgupta and Wahed, 2013). The benign conditions where CA-

125 is found includes endometriosis, hepatic cirrhosis, heart failure, fibroid uterus, acute salpingitis, hepatopathy, pulmonary tuberculosis, peritoneal and pericardial infection. (Sahin and Yildiz, 2012). In the menstrual phase of the cycle in women, CA-125 values may be elevated, causing false-positive test results. CA-125 may also increase after abdominal surgery, chronic obstructive pulmonary disease, active tuberculosis, and lupus erythematous showing false positive result. The false-negative results were due to the presence of anti-idiotypic antibody (Al-Ibraheemi *et al.*, 2013).

Increased CA-125 levels in response to tuberculosis was first observed in 1980's in ascites from patients initially diagnosed with ovarian carcinoma (Yoshimura and Okamura, 1987). CA-125 was also shown to be present in normal mesothelial cells and in normal epithelium of trachea and airway tissue. Stimulation of these tissues increased the levels of CA-125 in various body fluids, including serum. CA-125 excreted in response to inflammation or to damage to these tissues (Sahin and Yildiz, 2012). It was reported that serum CA-125 levels were higher in patients with pulmonary and extra-pulmonary TB than healthy subject. Some studies found CA-125 as a useful biomarker to evaluate the response to treatment.

The reference value for normal serum CA-125 level is less than 35 U/mL. There is a wide range of cut-off values used by authors but in the majority of studies the most accurate threshold was found to range between 31-36 U/ mL. In an analytical study included 42 cases the cut-off level for accurate determination of activity was 36.35 U/mL (Sahin and Yildiz, 2012) and in another group pulmonary TB was the associated with Ca-125 level >32.5 U/ mL (Fortun *et al.*, 2009). The diagnostic usefulness of CA-125 depends on its

sensitivity and specificity. Many studies suggest that CA-125 can be a beneficial parameter in determination of pulmonary tuberculosis activity. The sensitivity of CA-125

level was found 97.6% and specificity was 100% by Füsun Şahin (Sahin and Yildiz, 2012). Similarly A.Yilmaz et al found the sensitivity and specificity of CA-125 in PTB were 97.5% and 100%, respectively, at a 31 U/ml cut-off point (Yilmaz *et al.*, 2001). But value is quite different in J. Fortún et al study, here sensitivity - 68.6% and specificity- 77.8% was found (Fortun *et al.*, 2009).

High level CA-125 can be considered in diagnosis or discrimination in active and inactive patient. In this issue, a study done by Sefa Levent Ozsahin et al showed the positive predictive value was 59% and negative predictive value was 67% (Ozsahin *et al.*, 2008). Whereas Azza Farag Said et al, found the positive, negative predictive value was 79.2% and 87.2%, respectively (Said *et al.*, 2013).

Most deaths from TB are preventable by early diagnosis and treatment. Studies showed extensive delay in TB diagnosis and treatment were severe. Hence, the crucial point to eradicate the disease is improving the diagnosis of tuberculosis. Besides this determination of pulmonary TB activity during treatment is also important. Usually chest radiography, sputum acid-fast staining, and mycobacterial cultures are used for evaluating therapeutic responses. But chest radiography improves slowly with treatment. Furthermore, sputum examination is impossible in some patients. In Turkey, to determine the role of CA 125 in diagnosis of PTB, a total of 146 patients were included among them 30 had active PTB, 37 inactive PTB, 28 community-acquired pneumonia (CAP), 25 pleural or pulmonary malignancies. Increased CA125 levels were detected in active PTB in the current results. The results also showed that high level CA125 should be reconsidered in the prediagnosis and/or discrimination of active and inactive PTB (Ozsahin *et al.*, 2008).

In china, a case-control study with 565 subjects, conducted by Jingjing MA et al, found that serum CA125 has potential good diagnostic performance for PTB. This study result showed that serum levels of CA125 in PTB patients were significantly higher than those in control group ($P<0.001$). The sensitivity and specificity of serum CA125 is 95.6% and 85.0% respectively. They also found that there was no significantly different of this tumor markers between initial treatment group and retreatment group (MA *et al.*, 2016).

To investigate the clinical significance of serum CA- 125 measurements in patients with active pulmonary tuberculosis Eun Sun Kim et al, conducted a study in Korea among 100 patient. Among them thirty-eight patients showed elevated CA-125 and the level of CA-125 decreased with anti-TB treatment ($p =0.001$). This study concluded that serum CA-125 was related to the activity and severity of pulmonary TB, and it may be useful in the monitoring of therapeutic responses in certain cases of active pulmonary TB, especially in female (Kim *et al.*, 2013)

Similarly, J. Fortún et al, found CA 125 has not only diagnostic value but also prognostic value. Study conducted on 98 patients among them 35 with pulmonary TB and 54 with other respiratory infections. Pulmonary TB was the only factor associated with a raised CA 125 level. In 10 patients with TB, CA 125 levels decreased during treatment. This study summarize that CA 125 values increase in patients with pulmonary TB and decline to normal values during treatment. In some cases it may be used in patients with a negative sputum AFB stain (Fortun *et al.*, 2009).

A study entitled with Serum CA-125: biomarker of pulmonary tuberculosis activity and evaluation of response to treatment, by Füsun Şahin and Pinar Yildiz was done. Here, the study investigate the ability of CA-125 to predict pulmonary tuberculosis activity. This analytical study included 42 cases with active tuberculosis, 35 cases with inactive tuberculosis and 20 healthy subjects. Result found that mean serum CA-125 level is significantly higher in TB patient that others. Of the 38 patients CA-125 levels decreased significantly after treatment. So results suggest that CA-125 is a beneficial parameter in determination of pulmonary tuberculosis activity and the evaluation of response to treatment (Sahin and Yildiz, 2012)

Tuberculosis remains one of the most deadly infectious diseases and has claimed millions of lives for many years. Although the Bangladesh National TB Control Program (NTP) covers 99% of the population but significant delays in care-seeking, diagnosis, treatment initiation and completion for drug-sensitive and drug-resistant TB remain. So more efforts are still needed.

III. Materials And Methods

3.1 Study design: Cross sectional Analytical study

3.2 Study place: Out and in-patient Dept. of Medicine, Rangpur Medical College Hospital, Rangpur.

3.3 Study period: From March 2018 to September 2019

3.4 Study population: Patients attending in the Department of Medicine in Rangpur Medical College Hospital, Rangpur, with the diagnosis of Pulmonary Tuberculosis either smear positive or smear negative X pert MTB/RIF positive

3.5.1 Inclusion criteria:

- Smear positive pulmonary tuberculosis patients
- Smear negative X pert MTB/RIF positive patients
- Patients 18 years or above

3.5.2 Exclusion criteria:

- Patients getting anti tubercular therapy irrespective of duration
- Known malignancy anywhere
- Patient with benign gynaecological lesions (eg: PID, endometriosis)
- Pregnancy

- Menstruating women
- Liver cirrhosis
- Heart failure
- Renal failure

3.6 Sample size

Sample size, $n= z^2pq/e^2$

Here, z=1.96

p=0.5 (an approximate prevalence is used as exact prevalence is not known)

q=0.5

e=0.08

So, estimated sample size is, n=150

Since the exact prevalence of serum CA125 level in Pulmonary Tuberculosis patient is unknown, so for convenience 100 patients were taken in this study among which 50 patients with Smear positive Pulmonary Tuberculosis & 50 patients with smear negative X pert positive Pulmonary Tuberculosis.

3.7 Sampling technique

Sampling technique was purposive

3.8 Data collection technique

This study was performed at department of Medicine, Rangpur Medical College Hospital,Rangpur from March 2018 to September 2019. This study was approved by the ethical review committee of Rangpur Medical College. A written informed consent was obtained from patients. Total hundred subjects participated in this study and were divided into the following groups: Group A – Case of Smear positive Pulmonary Tuberculosis and Group B – Case of Smear negative Xpert MTB/RIF positive Pulmonary Tuberculosis. Before inclusion, all patients were screened in according to the inclusion and exclusion criteria. Data were collected by face-to-face interview and by review of the laboratory record register using a structured interviewer-administered questionnaire. The questionnaire was developed and approved by the study supervisor and the ethics committee. It was then piloted at the department of medicine during the month of July 2018. The purpose of the pilot was to determine the feasibility of the sampling, whether the question can measure the variables of the study objectives, and the flow and the appropriate wordings of questions contained in the data collection tool. The questionnaire was standardized before data collection. Patients' interviews were carried out by the researcher himself (me) working at the study site. The interviews were conducted at the hospital in a relaxed and conducive atmosphere. All data collection procedure was supervised by the guide and co-guide. The variables that were considered in this study included characteristics of the patient (Age, Sex), patient related factors

(having a member of family taking care of patient, history of TB contact, sputum smear examination result, existence of underlying condition) and drug related factors (history of previous TB treatment, use of traditional medicines or herbs, history of TB drug side effects, treatment delay). In this study, incomplete or incorrectly completed data sheet was discarded and a new patient was recruited by following above mentioned procedure. Following confirmation, CA-125 level was estimated for each patient. Collected data were recorded into the separate case record form. Finally, data analysis were done be the SPSS version 23 and result were describe by descriptive statistics. P-value <0.05 was considered statistically significant in this study.

3.9 Data Collection Tools

- A semi-structured questionnaire and checklist
- Tools for physical exam
- Informed written consent form in Bangla
- Informed written consent form in English

3.10 Data processing and analysis

After collection of all the required data, these were checked, verified for consistency and then tabulated into the computer using the Package for Social Sciences (SPSS Inc., Chicago, IL, version 23.0 for Windows). Normality of data were checked by measures of Kolmogorov–Smirnov tests of normality. Qualitative or categorical variables were described as frequencies and proportions. Chi-square test was done to determine the relationship between two variables. All statistical tests were two-sided and performed at a significance level of p =<0.05.

3.11 Ethical consideration

Basic principle of research ethics according to 52 th WMA declaration of Helsinki-2000 and CIOMS guide lines was maintained during the research processes. An ethical clearance certificate was taken from concerned authorities of the institute.

After selection of the subjects for study my introduction was given to all subjects as per declaration form. Before going to the procedure, all patients were explained about the nature of the study in easily understandable local language. They were ensured that their privacy will be maintained properly and all their information will be dealt confidentially. It was ensured that the study will not cause any social, economic or psychological harm to the patient and treatment would not be hampered for this. Patient can withdraw himself/herself from this research work at any moment. After understanding everything, if a subject gives informed written consent, only then he/she will be included in this study (according to consent form).

IV. Results

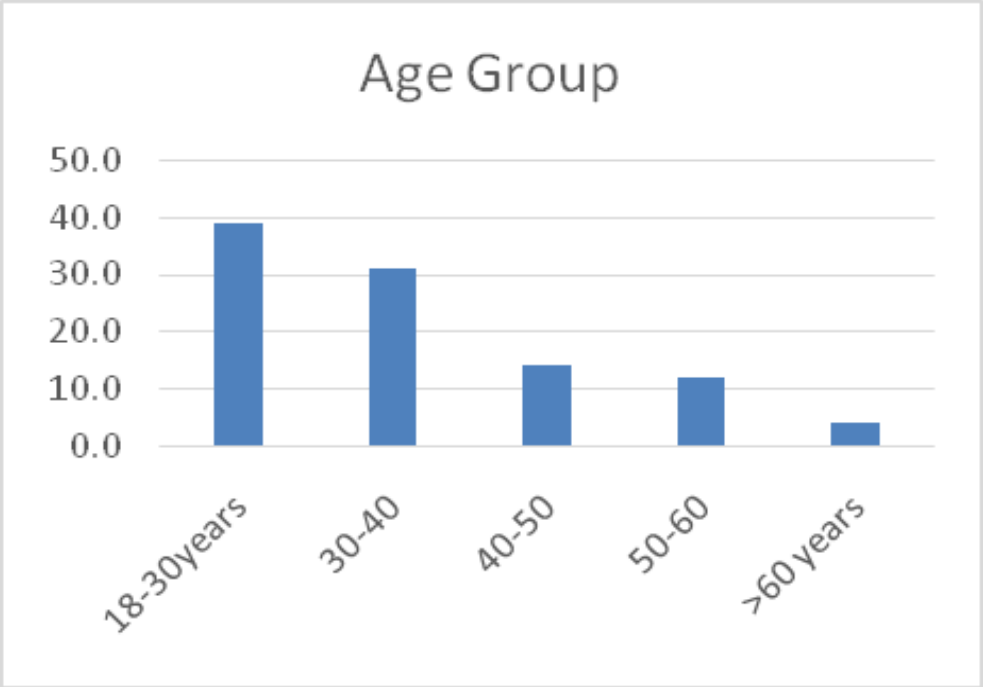

Figure-I: Distribution of study population according to age group. (N=100)

Figure-I demonstrates that out of 100 patients with tuberculosis, majority were in the 18-30 years group (39%) followed by 31% in 31-40 years group. That means, 70% of total study subjects were <40 years old.

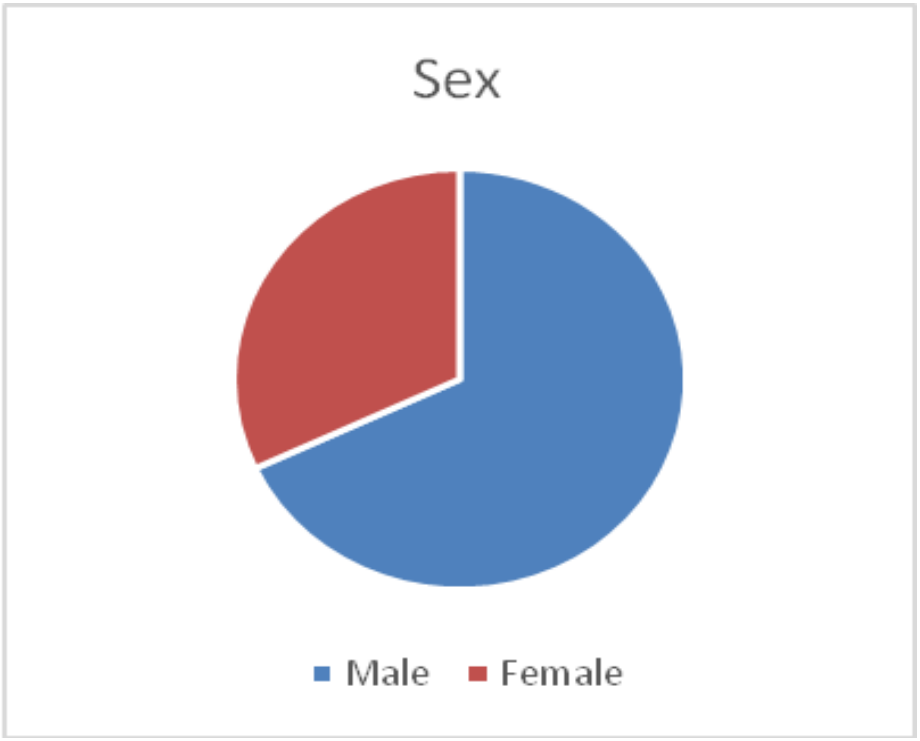

Figure-II: Gender distribution of study population (N=100)

Out of 100 patients, 68% were male and 32% were female. Male female ratio was 2.13:1.

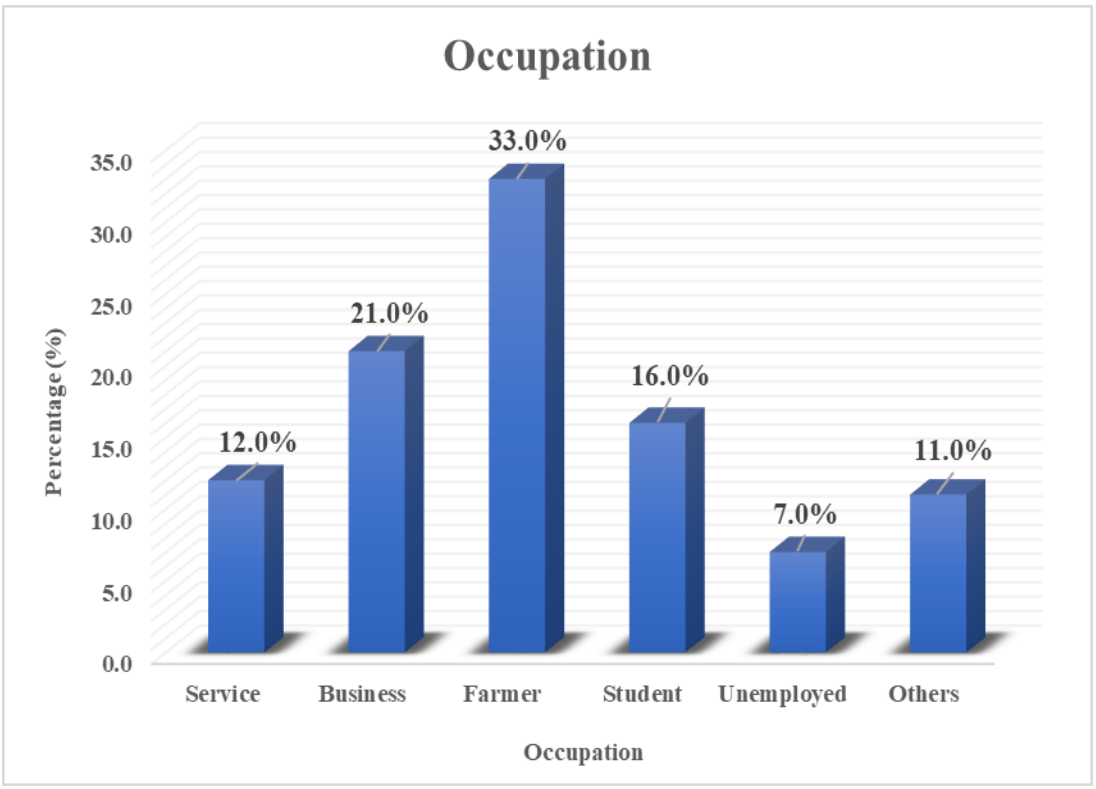

Figure-III: Distribution of the study population according to occupation (N=100)

Out of 100 patients, majority (33%) were farmer, 21% were businessman, 16% were students.

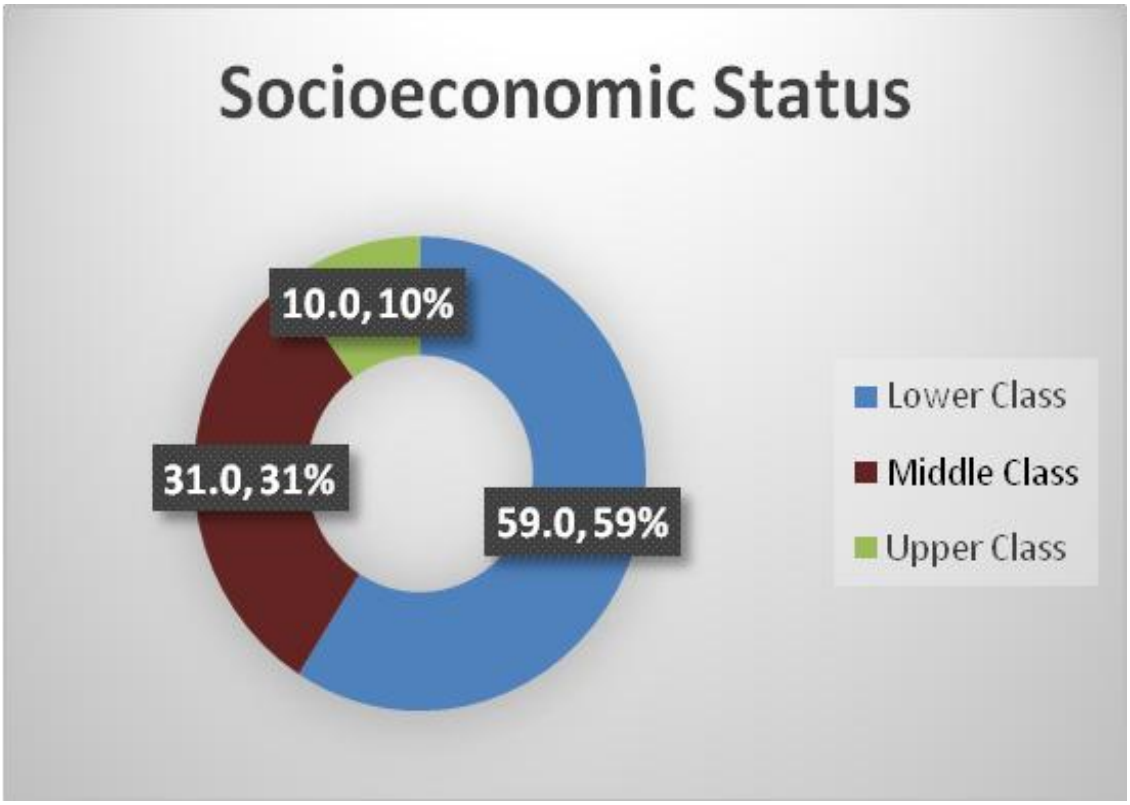

Figure-IV: Distribution of the study population according to their socio-economic status (N=100)

Among 100 TB patients of our study, 59% were from lower socioeconomic family while only 10% from upper class status.

Table-I: Other characteristics of Tuberculosis patients of our study (N=100).

Variables	Frequency	Percentage
Smoking history		
Yes	61	61.0%
No	39	39.0%
Alcohol consumption		
Yes	12	12.0%
No	88	88.0%
History of DM		
Yes	26	26.0%
No	74	74.0%

61% patients were smoker, 26% had DM and only 12% drink alcohol among 100 study population.

Table-II: Clinical presentation of pulmonary tuberculosis patients of our study (N=100).

Clinical presentations	Frequency	Percentage
Cough with expectoration	100	100.0%
Low grade fever	72	72.0%
Chills	53	53.0%
Sweating	41	41.0%
Weight loss	65	65.0%
Anorexia	71	71.0%

Above table is showing clinical presentations of our study population. Cough with expectoration was the commonest presentation seen in 100% patients. It is followed by, low grade fever in 72%, chills in 53%, seating in 41% and weight loss in 65% patients.

Table-III: Examination findings of study population (N=100).

Findings	Frequency	Percentage
Normal Chest	94	94%
Pleural effusion	6	6%
Anaemia	42	42%
Tachycardia	54	54%
Hypotension	14	14%

Physical examination findings of study population show, 94% had normal chest and 6% patients had pleural effusion. 42% patients had anaemia, 54% had increased pulse rate.

Table-IV: Different characteristics of sputum smear positive cases according to serum CA-125 levels (N=50).

Variables	Smear positive cases (Serum CA-125 ≥ 35 IU/mL)
Frequency	50 (100%)
Mean Age (years)	33.08±9.75
Mean Serum CA-125	74.69±49.51 IU/mL
Minimum	37 IU/mL
Maximum	153 IU/Ml

Different characteristics of sputum smear positive cases showed, out of 50 smear positive cases, all had Serum CA-125 ≥ 35 IU/mL. The mean age as, 33.08±9.75 years. Mean serum CA-125 was 74.69±49.51 IU/mL.

Table-V: Different characteristics of sputum smear negative gene Xpert positive cases according to serum CA-125 levels (N=50).

Variables	Smear negative gene Xpert positive cases	
	Serum CA-125 < 35 IU/mL	Serum CA-125 ≥ 35 IU/mL
Frequency	12 (24%)	38 (76%)
Mean Age (years)	33.00±11.66	42.58±14.10
Mean Serum CA-125	19.73±11.86 IU/mL	134.51±86.74 IU/mL
Maximum	33.3 IU/mL	309 IU/mL
Minimum	5.5 IU/mL	45 IU/mL

Among 50 smear negative gene Xpert positive cases, 24% had serum CA-125 level <35 IU/mL and rest 76% had ≥35 IU/mL. In the first group, mean age was, 33.00±11.66 years, mean serum CA-125 was 19.73±11.86 IU/mL. In the second group, mean age was 42.58±14.10 years and mean serum CA-125 was 134.51±86.74 IU/mL.

Table-VI: Measurement of serum CA-125 level of pulmonary tuberculosis patients of our study (N=100).

CA-125 level	Frequency	Percentage
Normal (<35 IU/mL)	12	12.0%
Elevated (≥35 IU/mL)	88	88.0%
Mean ± SD	90.82 ± 74.28 IU/mL	
Minimum	5.50 IU/mL	
Maximum	309 IU/mL	

According to the above table, majority of the PTB patients (88%) had elevated serum CA-125 level (≥35 IU/mL). The mean serum CA-125 was 90.82 ± 74.28 IU/mL, minimum as 5.50 IU/mL and maximum were 309 IU/mL.

Table-VII: Comparison of Serum CA-125 level in between smear positive cases and smear negative, gene Xpert positive cases of pulmonary tuberculosis (N=100).

Serum CA-125	Group-I (Smear positive cases)	Group- (Smear negative & gene Xpert positive cases)	P-value
<35 IU/mL	0	12 (24%)	
≥35 IU/mL	50 (100%)	38 (76%)	<0.001*
Total	**50 (100%)**	**50 (100%)**	
Mean ± SD	74.69 ± 49.51	106.96 ± 90.35	0.029**

***P-value <0.001, ** P-value <0.05**

Smear negative & gene Xpert positive cases has statistically significant higher level of CA-125 cases in comparison to smear positive cases (P-value <0.05 in both test).

V. Discussion

Pulmonary tuberculosis (TB) is one of the leading causes of mortality worldwide and has become a global public health emergency (Edwin Kendig, 1990). It is the leading cause of death after HIV from infectious diseases (Corbett *et al.*, 2003; World Health Organization, 2008). Cancer Antigen 125 (CA-125) is a high molecular weight glycoprotein that is expressed on the epithelial cells of the fallopian tube, endometrium, and mesothelial cells lining the pleura, pericardium, and peritoneum (Kabawat *et al.*, 1983). CA-125 levels are elevated in a number of malignant diseases such as those involving the ovaries, lungs, breasts, colon, pancreas, and in some non-malignant conditions including endometriosis, hepatic cirrhosis or heart failure. However, there have been few reports on the relationship between the activity of pulmonary TB and CA-125 levels (Yilmaz *et al.*, 2001). This study was done to see the role of serum CA-125 level in diagnosis of pulmonary tuberculosis in 100 cases of tuberculosis.

According to Figure – I : Among 100 study population, the minimum and maximum age were 19 years and 65 years respectively. The highest prevalence of tuberculosis was observed in 18-30 years age group (39%) followed by 31% in 30-40 years. That means, about 70% patients with TB were below 40 years of age in our study. They are the most physically active age group. So, such infection of this group may cause a strong economic burden and affect their working potentiality. Similar age-wise distribution of TB patients was also found in the study conducted by Kaur et al. who found that the maximum patients, that is 55.9% of patients belong to 15– 30 years (Kaur *et al.*, 2013). A study conducted by Sarkar et al. also found that the maximum 79.1% patients belonged to 15–54 years of age group (Sarkar *et al.*, 2007). Hence such age-wise distribution is also supported by many other studies like Kolappan et al. in their study in Tiruvallur district in Tamil Nadu was also found that majority 47.4% patients were 15–34 Years of old (Kolappan *et al.*, 2013).

According to Figure – II : With regard to gender, higher prevalence of tuberculosis in male (68%) than female was observed. In a study by Nirupa C et al., on 285 patients, 68% were male and rest 32% females, which is exactly same to the present study (Nirupa *et al.*, 2005). In a study by Mohammad Tahir et al., the proportion of male patients was about 57% and remaining 43% female (Tahir *et al.*, 2006). This proportion in males is lower than that of present study and these differences could be due to regional and cultural differences. The higher proportions of male in almost all of the above studies could be because of their higher chances of exposure to sources of TB infection.

According to Figure – III : Majority 33% were farmers followed by businessman 21%. So, disease was more common in worker groups. Similarly, in a study conducted by Pandit et al. at Anand district of Gujarat also found that 47.9% TB patients were laborers (Pandit and Choudhary, 2006). In Bangladesh the highest proportion of the MDR-TB cases (61.2%) were in occupations like agriculture, production and transport which was also supportive to us (Flora *et al.*, 2013). Employment status affects the treatment outcome as well as treatment adherence.

According to Figure – IV : Among 100 patients of our study, majority (59%) were from low socio-economic group followed by 31% in middle class group. A study from China showed that lower socio-economic status was associated with increased vulnerability to tuberculosis (Collaboration, 2004). Unemployment, lower educational level, unhealthy living environment and overcrowding etc. may be reason for TB in lower class.

According to Table – I : 61% of the patients were smoker which is comparable with Raza et al. suggesting smoking is one of the main risk factors of TB (Raza, Rahman and Nahar, 2016). Alcohol consumption history was found in only 12% patient as our society doesn't allow alcohol openly. A study in a developing country suggested that the main risk factor for TB was smoking. Furthermore, behavioral factors especially cigarette smoking and alcohol use have negative effect on TB treatment. Cigarette smoking is known to damage the lungs and suppress the individual adaptive immune responses affecting patient's response to TB treatment and alcohol suppresses the immune response and alcoholics are more likely to forget taking their treatment and hospital appointments leading to interruptions.

According to Table – II & III : The most common symptoms observed in pulmonary tuberculosis patients were cough with expectoration (100%) followed by low grade fever (72%), Anorexia (71%) and weight loss in 65% patients.

Physical examination findings showed, 94% patients had normal chest and 6% had pleural effusion. 42% patients had anaemia on examination. Raza et al. and Sajith et al. also found cough as the typical symptoms of tuberculosis in their studies (Sajith *et al.*, 2015; Raza *et al.*, 2016).

According to Table – IV,V&VI : Our study population comprised of two groups of patients; group-1 smear positive cases 50 and group-2 smear negative gene Xpert positive cases 50. Among 50 group-1 patients, all were smear positive. The mean age was 33.08±9.75 years. Their mean serum CA-125 level was 74.69±49.51 IU/mL. In 50 group-2 patients, 24% had serum CA-125 were normal (<35 IU/mL) and rest 76% had elevated CA-125 level. The mean age in the normal CA-125 patients was 33±11.66 years and mean serum CA-125 level 19.73±11.86 IU/mL.

These results were in agreement with those of, Yilmaz et al. who studied the value of CA-125 in the evaluation of tuberculosis activity and found that serum CA-125 levels were higher in patients with pulmonary and extra-pulmonary TB than in healthy subjects (Yilmaz *et al.*, 2001). These results were also in agreement with those of Said et al. who found that mean CA 125 levels were significantly higher among patients with active pulmonary tuberculosis (93.5±138.9 IU/ml) compared to healthy controls (10.5±7.3, P = 0.004) (Said *et al.*, 2013).

Again, In group-1 smear positive all patients had elevated CA-125 level, among group-2 smear negative Xpert positive cases, 24% patients had normal serum CA-125 level while 76% had elevated level of CA-125. This study is statistically significant. The mean value in both groups was 74.69 ± 49.51 IU/mL and 106.96 ± 90.35 IU/mL respectively which was also statistically significant. The possible cause of normal serum CA-125 level in group-2 patients was getting treatment for TB. In a study conducted in Japan, high serum levels of CA-125 were detected in 45% of the 40 patients with active pulmonary

Tuberculosis (Huang *et al.*, 2011).

According to Table – VII : In the cases of sputum negative but gene Xpert positive patients, we clearly found elevated serum CA-125 level. So, high serum CA-125 levels may be useful for detecting tuberculous activity in uncertain cases, in cases with negative sputum for AFB or in cases for which a sputum examination cannot be performed. Fortún et al. also concluded that, CA-125 measurement may be recommended if pulmonary tuberculosis is suspected and AFB stain of respiratory samples is negative or not available (Fortun *et al.*, 2009). To conclude, raised serum CA-125 is a good diagnostic tool for clinically suspected but smear negative pulmonary tuberculosis patients.

VI. Conclusion:

Increased CA-125 level was found in almost ninety percent of the patients. The level of CA-125 is significantly higher in smear negative Xpert positive cases. Bases on the findings, it can be said that CA-125 has potential to be a diagnostic tool in both pulmonary TB cases that need to be tested further.

6.2 Limitations

There were a number of limitations of the study, which includes:

- Sample size was small
- All samples were collected from a single study site
- No control groups were added
- Extrapulmonary TB cases were not considered
- Follow up of the patients were beyond the scope of the study

6.3 Recommendation:

- Serum CA-125 could be used as a tool in the diagnosis of Pulmonary TB
- Further study with appropriate study design is recommended

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